For reference, see the official NIAID Clinical Terms of Award.

Guidance for Compliance with NIAID Clinical Terms of Award

I. Overview

The National Institute of Allergy and Infectious Diseases (NIAID) supports clinical trials and studies involving human subjects and must ensure compliance with federal regulations including procedures to protect the safety of all participants. To assist NIAID in properly monitoring studies, additional information is required beyond what is normally submitted with a competitive application or proposal and the annual noncompetitive renewal application or annual progress report. These NIAID requirements are consistent with and complementary to requirements stated in the instructions for the PHS 398 Grant Application and PHS 2590 Non-Competing Grant Progress Report and in NIAID requests for proposals, requests for applications, and program announcements.

The NIAID Clinical Terms of Award apply to all NIAID-supported clinical research involving human subjects including single site, multicenter, U.S. domestic, multinational, and international clinical trials or clinical research.* Human subjects research includes the following:

- Development of new technologies using human subjects or materials derived from patients or volunteers.
- Studies into the mechanisms of human disease using patient or volunteer samples.
- Therapeutic interventions, clinical trials, and any studies that require institutional review board (IRB) or independent ethics committee (IEC) approval to collect samples from patients or volunteers.
- Epidemiologic and behavioral studies.
- Outcomes and health services research.

These Clinical Terms of Award delineate the awardee's responsibilities for submitting the required documentation to NIAID (and other NIH offices, as applicable) and will be summarized and attached to the notice of grant award or addressed in the terms of the contract. Once notified of the award, the responsible NIAID program or project officer will advise the awardee to begin the submission process. All submissions required by the NIAID Clinical Terms of Award must be forwarded electronically or by mail to the responsible NIAID program or project officer, according to the review mechanisms applicable to the awarding division. The Clinical Terms of Award define timelines related to the initiation of the human subjects research and reporting events related to the progress of the protocol. It is the awardee's responsibility to submit the required documentation to NIAID according to these timelines.

All clinical research supported by NIAID must comply with U.S. state and local regulations. All clinical research supported by NIAID that is conducted outside the U.S. must also comply with local regulations of the host country. Whenever the regulations differ between authorities, the more restrictive regulation will apply.

Applicants for clinical research must comply with these policies and guidelines in the preparation of their applications and proposals. At the end of this document is a checklist of submission and ongoing reporting requirements.

***** Note: These terms apply to each identifiable study supported by the award.

II. Requirements at Time of Proposal and Competitive Application

Applicants for clinical research must assure adherence to applicable regulations and guidelines by including the following in the proposal or application.

1) Research plan, including protocol (if required by the division)

2) Data and safety monitoring plan for clinical trials

Independent monitoring is essential for all clinical trials involving investigational drugs, devices, or biologics and other clinical research perceived to involve more than a minimal risk. Data and safety monitoring is intended to provide an independent objective review of the conduct of the research, interim safety and efficacy data, and progress towards achieving the goals of the study.

NIH policies require:

- Applications and proposals that propose studies with more than minimal risk to human participants include a plan for data and safety monitoring.
- Protocols for clinical trials include detailed plans for monitoring.
- Phase III trials have an independent data and safety monitoring board (DSMB).

Monitoring plans must be included in any application or proposal that proposes research involving more than minimal risk.

3) Targeted Enrollment

A "Targeted/Planned Enrollment Table" must be submitted with the PHS 398 grant application or contract proposal. The table includes projected accrual and demographic information of the study population. The format for the "Targeted/Planned Enrollment Table" is at http://grants.nih.gov/grants/funding/phs398/enrollment.rtf and http://grants1.nih.gov/grants/funding/phs398/enrollment.pdf; links to all grant application forms are at http://grants.nih.gov/grants/funding/phs398/phs398.html.

III. Submission Requirements Before Study Enrollment

Before the actual conduct of the study, the awardee will submit the following (as applicable) to the responsible NIAID program or project officer for review and approval according to the review mechanisms applicable to the awarding division.

1) Clinical Protocol

The awardee will submit the IRB- or IEC-approved protocol identified by version number, date, or both, including details of study design, proposed interventions, patient eligibility, and exclusion criteria. Unless otherwise directed, the clinical protocol will be required by NIAID before enrollment of participants begins.

A protocol for a clinical trial must adhere to International Conference on Harmonisation E6: Good Clinical Practices, Section 6, and must address the following issues related to safety.

- Plans for managing side effects.
- Procedures for assessing and reporting adverse events.
- Plans for data and safety monitoring and monitoring of the clinical study site, pharmacy, and laboratory.

2) Institutional Review Board or Independent Ethics Committee Approval

The awardee is responsible for submitting all IRB or IEC notifications of protocol approval to the responsible NIAID program or project officer, including the name of the IRB or IEC, its Office of Human Research Protection (OHRP) registration number, and OHRP federal-wide assurance number. Where other institutions are involved in the research, e.g., a multicenter study, the protocol should be reviewed and approved by each institution's IRB or IEC. Written documentation of approval from each institution must be provided to NIAID and must include a copy of the IRB- or IEC-approved informed consent document identified by version number, date, or both and dates it is valid.

Some countries have a national IRB or IEC for which protocol and informed consent approval may be required. This approval process may be in addition to or in lieu of local IRB or IEC approval. For countries with multiple levels of IRB review, written documentation of protocol approval from each IRB must be provided to NIAID, along with a copy of the IRB or IEC approved informed consent document, identified by version number, date, or both and dates it is valid.

3) Data and Safety Monitoring

Monitoring plans must be included in any application or proposal for research involving more than minimal risk. However, final decisions regarding the type of monitoring to be employed will be made jointly by NIAID and the awardee prior to study initiation. Discussions with the responsible NIAID program or project officer regarding appropriate safety monitoring and approval of the final monitoring plan by NIAID will occur before patient enrollment begins and may include discussions about the appointment of one of the following.

- **Independent Safety Monitor –** a physician or other appropriate expert who is independent of the study and available in real time to review and recommend appropriate action regarding adverse events and other safety issues.
- **Independent Monitoring Committee (IMC) or Safety Monitoring Committee (SMC)** – a small group of independent investigators and biostatisticians who review data from a particular study.
- **Data and Safety Monitoring Board (DSMB)** – an independent committee charged with reviewing safety and trial progress and providing advice with respect to study continuation, modification, and termination. The awardee may be required to use an established NIAID DSMB or to organize an independent DSMB. All phase III clinical trials must be reviewed by a DSMB; other trials may require DSMB oversight as well.

When a monitor or monitoring board is organized by the awardee, a description of the monitor or board, and its charter, operating procedures, or both (including proposed

meeting schedule and plan for review of adverse events), and roster and *curriculum vitae* from all members must be submitted to and approved by NIAID before to study initiation.

4) Investigational New Drug or Investigational Device Exemption Requirements

Consistent with federal regulations, clinical research projects in humans involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products or devices used for a purpose other than that for which they were licensed) under a research protocol should be performed under a U.S. Food and Drug Administration (FDA) IND or IDE. Exceptions must be granted in writing by FDA. If the proposed clinical trial will be performed under an IND or IDE, the awardee must provide NIAID with the name and institution of the IND or IDE sponsor, the date the IND or IDE was filed with the FDA, the FDA IND or IDE number, any written comments from the FDA, and the written responses to those comments. In addition, submit risk information (e.g., product development plan, investigator's brochure, or information obtained through published literature review or other venue).

The awardee must wait 30 days from FDA receipt of initial IND or IDE application before initiating the clinical trial. The awardee must notify NIAID if FDA places the study on clinical hold and provide NIAID any written comments from FDA, written responses to the comments, and documentation in writing that the hold has been lifted.

For all intervention studies, the awardee must obtain regulatory oversight by either FDA (under an IND or IDE) or the regulatory body of the country where the research is to be conducted. In the case of a foreign regulatory body, the awardee must provide NIAID with written documentation from the regulatory body that the awardee is in compliance with local regulatory laws.

5) Recombinant DNA Advisory Committee

For clinical trials involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human research participants (human gene transfer), the awardee must provide NIAID written documentation that the NIH Office of Biotechnology Activities (OBA) Recombinant DNA Advisory Committee (RAC) review process has been completed and that institutional biosafety committee approval (from the clinical trial site) has been obtained. See the NIH Guidelines for Research Involving Recombinant DNA Molecules at http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html.

6) Requirements for Training in Human Subjects Protections

The awardee is responsible for submitting written documentation to NIAID that the awardee and all study staff responsible for the design or conduct of the research have received training in the protection of human subjects.

7) Other Requirements

Other requirements may be determined on a case-by-case basis. NIAID and the awardee must document the requests for and compliance with these additional requirements.

In accordance with the NIAID review process, NIAID staff comments will be forwarded to the awardee within three weeks of receipt of the above information. The awardee must address in writing all safety, regulatory, ethical, and conflict of interest concerns raised by NIAID staff to the satisfaction of NIAID before participant enrollment can begin. Any changes to the protocol must be reviewed and approved by the IRB or IEC prior to participant enrollment.

IV.Ongoing Reporting Requirements

Awardees must comply with all Clinical Terms of Award throughout the course of the clinical research. These requirements include the following.

1) Institutional Review Board or Independent Ethics Committee Actions

Unless otherwise directed, the awardee is responsible for submitting to NIAID all IRB or IEC notifications of protocol renewal, amendment, suspension, and termination. Where other institutions are involved in the research (e.g., a multicenter study), the protocol should be reviewed and approved by each institution's IRB or IEC. The IRB for each site will conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year, as described in 45 CFR 46.109.

a) Continuing review and approval

The awardee is required to submit to the responsible NIAID program or project officer (and contracting officer, if applicable) documentation of the continuing IRB or IEC review and approval annually, at a minimum. The submission will include the following.

- A copy of the IRB or IEC letter of renewal.
- A copy of the current IRB or IEC approved protocol, identified by version number, date, or both (unless otherwise directed).
- A copy of the current IRB or IEC approved informed consent document, identified by version number, date, or both and dates it is valid.

For countries with multiple levels of IRB review, written documentation of protocol review and approval from each IRB should be provided to the NIAID, along with a copy of the IRB- or IEC-approved informed consent document, identified by version number, date, or both and dates it is valid.

b) Amendment, suspension, termination

The awardee is required to submit to the responsible NIAID program officer (and contracting officer, if applicable) written documentation of any changes in IRB or IEC approval status, including the following.

- All amendments or changes to the protocol, identified by version number, date, or both. (Except in the case of imminent danger to participants, changes to the protocol must be approved by the IRB or IEC prior to clinical implementation.)
- All changes in informed consent documents, identified by version number, date, or both. Changes must be approved by the IRB or IEC before clinical implementation.
- Termination or temporary suspension of patient accrual.
- Termination or temporary suspension of the protocol.
- Any change in IRB or IEC approval status.
- Any other problems or issues that could affect the participants of the study.

Notification of any of the above changes must be made within three working days by email or fax, followed by a letter cosigned by the principal investigator and the institutional

business official, detailing the change of status notification to the IRB or IEC, and a copy of IRB or IEC responses.

2) Data and Safety Monitoring Reviews

When a monitor or monitoring board is organized, the awardee will submit written summaries of all reviews conducted by the monitoring group to the responsible NIAID program officer within 30 days of reviews or meetings. When reviews are frequent, semiannual or quarterly reports are sufficient.

3) Safety Reporting Requirements

a) IND or IDE reporting

The awardee must notify the responsible NIAID program or project officer in writing if the FDA places the study on clinical hold at any time during the conduct of the clinical trial.

b) IND or IDE safety reporting

Under the IND or IDE, the sponsor is required to provide the FDA with safety reports of serious adverse events. Under the Clinical Terms of Award, the awardee must submit copies to the responsible NIAID program officer as follows.

- *Expedited safety report of unexpected or life-threatening experience or death:* A copy of any report of unexpected or life-threatening experience or death associated with the use of an IND drug, which must be reported to FDA by telephone or fax as soon as possible but no later than seven days after the IND sponsor's receipt of the information, must be submitted to the NIAID program or project officer within 24 hours of FDA notification.
- *Expedited safety reports of serious and unexpected adverse experiences:* A copy of any report of unexpected and serious adverse experience associated with use of an IND drug or any finding from tests in laboratory animals that suggests a significant risk for human subjects, which must be reported in writing to FDA as soon as possible but no later than 15 days after the IND sponsor's receipt of the information, must be submitted to the NIAID program or project officer within 24 hours of FDA notification.
- *IDE reports of unanticipated adverse device effect:* A copy of any reports of unanticipated adverse device effect submitted to FDA must be submitted to the NIAID program or project officer within 24 hours of FDA notification; and
- *Expedited safety reports:* should be reported to the NIH Office of Biotechnology Activities concurrently with the report to FDA.
- Other adverse events documented during the course of the trial should be included in the annual IND or IDE report and reported to the NIAID annually.

In case of specific problems or issues, the NIAID program officer will contact the awardee within 10 working days (by email or fax), followed within 30 calendar days by an official letter to the principal investigator, with a copy to the institution's office of sponsored programs, enumerating issues and appropriate actions to be discussed.

- *Safety reporting for research not performed under an IND or IDE*

Final decisions regarding ongoing safety reporting requirements for research not performed under an IND or IDE will be made jointly by the NIAID and the awardee.

4) Recombinant DNA Advisory Committee and Institutional Biosafety Committee

The awardee submits to the NIAID program officer copies of the adverse event and annual reports required by NIH Office of Biotechnology Activities and by the site IBC, if applicable.

5) Requirements for Training in Human Subjects Protections

The awardee is required to submit documentation in the annual progress report that newly hired study staff responsible for the design or conduct of the research have received training in the protection of human subjects.

6) Inclusion Enrollment Reports

The "Inclusion Enrollment Report" includes cumulative accrual and demographic information for human subjects enrolled in the clinical research protocol. This report must be submitted annually. The annual submission of the enrollment report will coincide with each noncompeting renewal or annual progress report. The "Inclusion Enrollment Report" (Form PHS 398/2590) is located at both:

- http://grants.nih.gov/grants/funding/phs398/398_forms.pdf
  ftp://grants.nih.gov/forms/398_forms.pdf

Click on "Inclusion Enrollment Report" in the left-hand column under bookmarks.

7) Other requirements

Other requirements may be determined on a case-by-case basis. NIAID and the awardee must document requests for and compliance with these additional requirements.

NIAID Clinical Terms of Award Checklist

This checklist serves as a reminder of information that must be submitted to NIAID. This checklist may be completed by the investigator and attached to a submission to the responsible program or project officer according to the review mechanisms applicable to the awarding division.

Principal Investigator: Date:

Phone:

Fax:

Email:

Grant or Contract Number:

Site Name:

Address:

Protocol Title:

OHRP IRB or IEC Registration Number and Name:

Requirements at Time of Competitive Application and Proposal

☐ The research plan, including protocol, if required by the division.

☐ Data and safety monitoring plan, if applicable.

☐ Targeted/Planned Enrollment Table.

Requirements Before Study Enrollment

☐ IRB or IEC documents and protocol or protocols, identified by version number, date, or both; attach the following for each investigative site or IRB.

- IRB or IEC name.
- Federal-wide assurance number for institution or site.
- IRB or IEC OHRP registration number.
- IRB or IEC notification of protocol approval.
- IRB or IEC approved protocol.
- IRB or IEC approved consent forms identified by dates valid.

☐ ISM, SMC, or DSMB information, if applicable (attach charter, operating procedures, proposed roster and CVs).

☐ Additional information for clinical trials with INDs or IDEs.

☐ Name, institution, and address of IND or IDE sponsor.

☐ FDA IND or IDE number (attach copy of letter from FDA).

☐ FDA correspondence (attach copies of all written communication with FDA).

☐ Risk information (e.g., investigator's brochure, or information obtained through published literature review or other venue).

☐ Safety reporting for research not performed under an IND or IDE.

☐ Additional information for gene transfer clinical trials.

☐ NIH Recombinant DNA Advisory Committee initial review.

☐ Date of letter from OBA: _____ NA_____

☐ Public RAC review: Yes____ No:____

Include copy of letter from the Office of Biotechnology Activities either:

1) Stating the protocol has been exempted from public review.

2) Summarizing the RAC suggestions and PI response to the recommendations.

☐ IBC-related documents for human gene transfer protocols.

☐ Name of institution IBC serves.

☐ Copy of written IBC approval of protocol.

☐ Copy of protocol approved by the IBC and IRB.

☐ Documentation of training in human subjects protection for all study staff responsible for design or conduct of the research.

Ongoing Reporting Requirements

☐ Documentation of IRB or IEC continuing reviews – attach the following for each investigative site.

- IRB or IEC OHRP registration number.
- OHRP federal-wide assurance number for site.
- IRB or IEC continuing review and approval.
- IRB or IEC approved consent form identified by version number, date, or both and dates it is valid.
- IRB or IEC approved protocol identified by version number, date, or both unless otherwise directed.
- Documents related to protocol amendments, suspensions, or termination.

Please note that for the duration of the award it is the responsibility of the awardee to notify NIAID of subsequent protocol amendments or changes in IRB or IEC approval status within three working days of IRB or IEC decision. Documents related to an amended protocol must be submitted to the NIAID prior to implementing changes, except in the case of imminent danger to participants.

☐ Data and safety monitoring reviews or summaries, if applicable – submit within 30 days of review or meeting.

☐ IND or IDE safety reports.

- ☐ For 7-day IND telephone or fax reports, send copy to NIAID program or project officer within 24 hours of FDA notification.
- ☐ For 15-day IND written reports, send copy to NIAID program or project officer within 24 hours of FDA notification.
- ☐ For IDE reports of adverse device effect, send copy to NIAID program or project officer within 24 hours of FDA notification.
- ☐ Report adverse events not included in expedited reports in the annual IND or IDE report.
- ☐ For safety reports for gene transfer clinical trials, send to OBA concurrently with the report to FDA.

☐ **Documentation for Gene Transfer Clinical Trials**

- ☐ Annual report and reports of adverse events reports not included in expedited reports to OBA.
- ☐ IBC continuing approval.

☐ Training in human subjects protection for new study staff, if applicable **–** submit annually to coincide with each noncompeting renewal or annual progress report.

☐ Inclusion enrollment reports **–** submit annually to coincide with each noncompeting renewal or annual progress report.

NIAID Points of Contact

General Inquiries

Direct general inquiries related to this notice:

Office of the Director
Division of Extramural Activities, NIAID
Telephone: (301) 496-7291
FAX: (301) 402-0369
E-mail: ac20a@nih.gov or jm80c@nih.gov

Grant or Contract Inquiries and Document Submission

Direct inquiries about a grant or contract to the appropriate NIAID program officer. All information and documentation required by the NIAID Clinical Terms of Award must be forwarded electronically or by mail to the responsible NIAID program or project officer according to the review mechanisms applicable to the awarding division.

Regulations and Guidelines

The NIAID Clinical Terms of Award conform with NIH policy on human subjects research and are consistent with and complementary to requirements stated in the instructions for the PHS 398 and 2590 grant applications, NIAID requests for proposals, requests for applications, and program announcements. NIAID-supported clinical research must adhere to applicable clinical research and human subject protection regulations and guidelines, including those listed below.

For help and advice in preparing a human subjects application, see our" How To Write a Human Subjects Application" tutorial, which shows how to plan and write your application, including how to prepare for and follow the policy requirements, at http://www.niaid.nih.gov/ncn/clinical/humansubjects/hs_01.htm.

Policy References

Office for Human Research Protections

All clinical research supported by NIAID must comply with OHRP requirements for human subject protection, informed consent, IRB or IEC registration, assurances and responsibilities, including ongoing review. See the OHRP Internet site at http://ohrp.osophs.dhhs.gov/polasur.htm.

Required Education in the Protection of Human Research Participants

All investigators receiving NIAID funds for research involving human subjects are required to receive education on the protection of human subjects. NIH provides an online tutorial, "Human Participant Protections Education for Research Teams" at http://cme.nci.nih.gov/. Note: Other non-NIH-supported training programs are also available. NIAID provides you a sample form letter to send with your application at http://www.niaid.nih.gov/ncn/clinical/humansubjects/sample_letter.htm.

Code of Federal Regulation Title 45 Part 46

All clinical research supported by NIAID must comply with applicable Parts of U.S. Code of Federal Regulations, Title 45, Part 46 "Protection of human subjects," http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm.

International Conference on Harmonisation Guidelines for Good Clinical Practice

All clinical trials supported by NIAID shall comply with ICH and GCP guidelines. See a complete list at http://www.ifpma.org/ich1.html. Find a direct link to the pdf version at http://www.fda.gov/cder/guidance/959fnl.pdf.

FDA Guidance Documents

Find guidance documents that represent the FDA's thinking on a particular subject at the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research Internet sites:

http://www.fda.gov/cder/guidance/index.htm

http://www.fda.gov/cber/guidelines.htm

For questions, consult the FDA Office for Good Clinical Practice, http://www.fda.gov/oc/gcp/.

Find FDA's Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators (1998), which represents the agency's current guidance on protection of human subjects of research at http://www.fda.gov/oc/ohrt/irbs/default.htm.

6) Requirements for Research Conducted Under an IND

NIAID-supported clinical trials conducted under an FDA IND application must comply with relevant parts of CFR Title 21.

Title 21, Part 50, "Protection of human subjects"
http://www.fda.gov/oc/ohrt/irbs/appendixb.html

Title 21, Part 54, "Financial disclosure by clinical investigators"
http://www.fda.gov/oc/guidance/financialdis.html

Title 21, Part 56, "Institutional review boards"
http://www.fda.gov/oc/ohrt/irbs/appendixc.html

Title 21, Part 312, "Investigational new drug application"
http://www.fda.gov/cber/ind/21cfr312.pdf

NIH Office of Biotechnology Activities

See the NIH Guidelines for Research Involving Recombinant DNA Molecules
http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html.
http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

Optional template for reporting adverse events to OBA
http://www4.od.nih.gov/oba/rac/AER_template.rtf

Help in Preparing a Human Subjects Application

For more help and advice in preparing a human subjects application, see our How To Write a Human Subjects Application tutorial that shows how to plan and write your application, including how to prepare for and follow the policy requirements, at http://www.niaid.nih.gov/ncn/clinical/humansubjects/hs_01.htm.